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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,905	03/23/2004	David Scheinberg	D6499	2406

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,905	SCHEINBERG ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7-15,18-34,37-49,51-53 and 55-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-5, 7-15, 18-34, 37-49, 51-53 and 55-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/29/2007 has been entered.

Claims 1-2, 4-5, 7-15, 18-34, 37-49, 51-53 and 55-61 are currently pending and under consideration.

Rejections Withdrawn:

The rejection of claims 1-2, 7-14, 16-17, 19-25, 27-33, 35-36, 38-43, 45-49, 51 and 55-61 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants Arguments.

New Rejections Necessitated by Amendment:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 7-11, 49, 51 and 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennel et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15: 235-244, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731).

Kennel et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate (abstract). The reference further teaches that while the isotope coupled to the targeting monoclonal

antibody delivers a tumorcidal dose to the lung, the radiotoxicity associated with decay daughter isotopes released from the target organ limit the effectiveness of the therapy (page 242, 2nd column, last paragraph). For example, Kennel et al. teach at necropsy, animals had total ablation of bone marrow cells, splenic atrophy, some damage to the lining of their stomachs and intestine and excess accumulation of undigested food in their stomachs (page 240, 1st column, paragraph bridging page 239).

Kennel et al. do not explicitly teach administering a competitive metal blocker such as bismuth subnitrate in combination with the ^{225}Ac conjugate.

Satoh et al. teach the effects of preinduction of metallotheionein (MT) by bismuth subnitrate (BSN) on the adverse effects and antitumor activity of γ–ray irradiation in mice (abstract). In particular, the reference teaches that oral administration of BSN markedly reduced the lethal effects and bone marrow damage γ-ray irradiation without compromising the tumor-reducing effect (page 1730, 1st column, last paragraph). As such, Satoh et al. teach that bismuth subnitrate pretreatment is an effective method for protection against side-effects in radiotherapy (abstract).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to modify the method taught by Kennel et al. to include bismuth subnitrate in view of the teachings of Satoh et al.. One would have been motivated to do so because Satoh et al. teach that bismuth subnitrate pretreatment is an effect method for protection against side-effects in radiotherapy. Thus, one of ordinary skill in the art would have a reasonable expectation of success that modifying the method taught by Kennel et al. to include bismuth subnitrate in view of the teachings of Satoh et al, one would achieve a method for reducing the radio toxicity associated with the ^{225}Ac conjugate such as bone marrow damage.

Claims 4, 52 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennel et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15: 235-244, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731), as applied to claims 1-2, 7-11, 49, 51 and 57-60 above, in further view of Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113, *of record*).

Kennel et al. in view of Satoh et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate in combination with bismuth subnitrate. In addition to the total ablation of bone

marrow cells, Kennel et al. teach immediately after organ harvest, the level of ^{213}Bi, the third decay daughter of ^{225}Ac, was found to be deficient in the lungs and to be in excess in the kidneys (page 239, 1st column paragraph to 2nd column).

Kennel et al. in view of Satoh et al. do not explicitly teach administering an adjuvant such as a dithiol chelate in combination with the ^{225}Ac conjugate and bismuth subnitrate.

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Kennel et al. in view of Satoh et al. to further include the administration of an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in view of Jones et al. teachings that DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. One would have been motivated to do so because as taught by Jones et al., administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac isotope bound to a HEHA-MAb 201B conjugate, one would achieve a method for reducing the accumulation of

^{213}Bi in the kidney.

Claims 5, 53 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennel et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15: 235-244, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731), as applied to claims 1-2, 7-11, 49, 51 and 57-60 above, in further view of Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60, *of record*) and Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113, *of record*).

Kennel et al. in view of Satoh et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate in combination with bismuth subnitrate. In addition to the total ablation of bone marrow cells, Kennel et al. teach immediately after organ harvest, the level of ^{213}Bi, the third decay daughter of ^{225}Ac, was found to be deficient in the lungs and to be in excess in the kidneys (page 239, 1st column paragraph to 2nd column).

Kennel et al. in view of Satoh et al. do not explicitly teach administering a diuretic such as furosemide in combination with the ^{225}Ac conjugate and bismuth subnitrate.

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Jones et al. teaches that that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made modify the method taught by Kennel et al. in view of Satoh et al. to further include the administration of furosemide in view of the teachings of Schilcher et al. and Jones et al.. One would have been motivated to do so because Jones et al. teaches that that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a diuretic such as

furosemide in combination with an ^{225}Ac conjugate comprising a functionalized chelate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney.

Claims 12 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennel et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15: 235-244, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731), as applied to claims 1-2, 7-11, 49, 51 and 57-60 above, in further view of McDevitt et al. (Science 2001; 294: 1537-1540, *of record*).

Kennel et al. in view of Satoh et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate in combination with bismuth subnitrate. In addition to the total ablation of bone marrow cells, Kennel et al. teach immediately after organ harvest, the level of ^{213}Bi, the third decay daughter of ^{225}Ac, was found to be deficient in the lungs and to be in excess in the kidneys (page 239, 1st column paragraph to 2nd column).

Kennel et al. in view of Satoh et al. do not explicitly teach treating leukemia.

McDevitt et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 1537, Abstract). With regards to the cancer, the reference teaches (page 1537, Abstract) that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Kennel et al. in view of Satoh et al. to treat leukemia in view of McDevitt et al.. One would have been motivated to do so because McDevitt et al. teaches that ^{225}Ac conjugate is effective at treating leukemia. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by Kennel et al. in view of Satoh et al. to treat leukemia in view of McDevitt et al, one would achieve a method treating leukemia.

Claims 1-2, 7-12, 49, 51 and 57-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheinberg et al. (US 2002/0058007, 2002, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731).

Scheinberg et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 2, paragraph 0016). With regards to the cancer, the publication teaches (page 4, paragraph 0037) that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regards to the ^{225}Ac conjugate, the publication teaches (page 2, paragraph 0017) that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. For example, Scheinberg et al. provides (page 2, paragraph 0021) an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Moreover, the publication discloses the toxicity of ^{225}Ac constructs, wherein histological analysis of deceased mice showed gastrointestinal mucosal sloughing and bond marrow hyplasia, consistent with severe radiotoxicity (column 8, paragraph 0097).

Scheinberg et al. does not explicitly teach administering a competitive metal blocker such as bismuth subnitrate in combination with the ^{225}Ac conjugate.

Satoh et al. teach the effects of preinduction of metallotheionein (MT) by bismuth subnitrate (BSN) on the adverse effects and antitumor activity of γ–ray irradiation in mice (abstract). In particular, the reference teaches that oral administration of BSN markedly reduced the lethal effects and bone marrow damage γ-ray irradiation without compromising the tumor-reducing effect (page 1730, 1st column, last paragraph). As such, Satoh et al. teach that bismuth subnitrate pretreatment is an effective method for protection against side-effects in radiotherapy (abstract).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to modify the method taught by Scheinberg et al. to include bismuth subnitrate in view of the teachings of Satoh et al.. One would have been motivated to do so because Satoh et al. teach that bismuth subnitrate pretreatment is an effect method for protection against side-effects in radiotherapy. Thus, one of ordinary skill in the art would have a reasonable expectation of success that modifying the method taught by Scheinberg et al. to include bismuth subnitrate in view of the teachings of Satoh et al, one would achieve a method for reducing the radio toxicity associated with the ^{225}Ac conjugate such as bone marrow damage.

Claims 4, 52 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheinberg et al. (US 2002/0058007, 2002, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731), as applied to claims 1-2, 7-12, 49, 51 and 57-61 above, in further view of Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113, *of record*).

Scheinberg et al. in view of Satoh et al. teach a method of treating cancer with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent in combination with bismuth subnitrate. In addition to bone marrow hyplasia, Scheinberg discloses the biodistribution of ^{225}Ac conjugates in tumor bearing mice, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi, e.g. *daughter of ^{225}Ac*, accumulation in the kidney as a result of decay of the daughters from nontargeted constructs (beginning on page 8, 2nd column, Example 9).

Scheinberg et al. in view of Satoh et al. do not explicitly teach administering an adjuvant such as a dithiol chelate in combination with the ^{225}Ac conjugate and bismuth subnitrate.

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Scheinberg et al. in view of Satoh et al. to

further include the administration of an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in view of Jones et al. teachings that DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. One would have been motivated to do so because as taught by Jones et al., administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac conjugate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney.

Claims 13-15, 18-34, 37-49, 51-53, 55-56 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheinberg et al. (US 2002/0058007, 2002, *of record*) in view of Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60, *of record*) and in further view of Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113, *of record*).

Scheinberg et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 2, paragraph 0016). With regards to the cancer, the publication teaches (page 4, paragraph 0037) that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regards to the ^{225}Ac conjugate, the publication teaches (page 2, paragraph 0017) that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. For example, Scheinberg et al. provides (page 2, paragraph 0021) an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Moreover, the publication discloses the toxicity of ^{225}Ac constructs, wherein histological analysis of deceased mice showed gastrointestinal mucosal sloughing and bond marrow hyplasia, consistent with severe radiotoxicity (column 8, paragraph 0097). In addition to bone marrow hyplasia, Scheinberg discloses the biodistribution of ^{225}Ac conjugates in tumor bearing mice, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi, e.g. *daughter of ^{225}Ac*, accumulation in the kidney as a result of decay of the daughters from nontargeted constructs (beginning on page 8, 2nd column, Example 9)

Scheinberg et al. does not explicitly teach administering a diuretic such as furosemide in

combination with the ^{225}Ac conjugate. Nor does Scheinberg et al. explicitly teach further administering a dithiol chelate in combination with the ^{225}Ac conjugate.

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Scheinberg et al. to include administration of one or both a diuretic or a dithiol chelator in view of the teachings Schilcher et al. and Jones et al. One would have been motivated to do so because Jones et al. teaches that that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by Scheinberg et al. to include administration of one or both a diuretic or a dithiol chelator in view of the teachings Schilcher et al. and Jones et al, one would achieve a method for reducing the

accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

Claims 13-15, 18-34, 37-49, 51-53, 55-56 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDevitt et al. (Science 2001; 294: 1537-1540, *of record*) in view of Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60, *of record*) and in further view of Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113, *of record*)

McDevitt et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 1537, Abstract). With regards to the cancer, the reference teaches (page 1537, Abstract) that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regards to the ^{225}Ac conjugate, the reference teaches (page 1538, 1st column, 2nd full paragraph) that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. For example, Scheinberg et al. provides (page 1538, 1st column, 2nd full paragraph) an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Moreover, the publication discloses the biodistribution of ^{225}Ac conjugates in tumor bearing mice, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi, e.g. *daughter of ^{225}Ac*, accumulation in the kidney as a result of decay of the daughters from nontargeted constructs (page 1538, Figure 1B).

McDevitt et al. does not explicitly teach administering a diuretic such as furosemide in combination with the ^{225}Ac conjugate. Nor does McDevitt et al. explicitly teach further administering a dithiol chelate in combination with the ^{225}Ac conjugate.

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from

radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by McDevitt et al. to include administration of one or both a diuretic or a dithiol chelator in view of the teachings Schilcher et al. and Jones et al. One would have been motivated to do so because because Jones et al. teaches that that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by McDevitt et al. to include administration of one or both a diuretic or a dithiol chelator in view of the teachings Schilcher et al. and Jones et al, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

Therefore, No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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